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**WO 01/85249 A1**

(54) Title: A CATHETER LOCK SOLUTION INCLUDING A PHOTO-OXIDANT

(57) Abstract: This invention relates to compositions, methods and devices relating to the infusion of a catheter lock solution into an indwelling catheter. Inventive compositions, methods and devices aid in diminishing the effects of infection in the catheters and occlusion of the catheters. An inventive lock solution includes an anticoagulant and a photo-oxidant, and preferably has a density suitable for retention of the solution in a catheter during the lock period.

**A CATHETER LOCK SOLUTION  
INCLUDING A PHOTO-OXIDANT**

5                   **REFERENCE TO RELATED APPLICATIONS**

          This application claims the benefit of U.S.  
Provisional Application No. 60/203,358, filed May 10,  
2000 and entitled A CATHETER LOCK SOLUTION INCLUDING A  
PHOTO-OXIDANT, which is hereby incorporated by reference  
10   herein in its entirety.

**BACKGROUND OF THE INVENTION**

          This invention generally relates to catheters and  
15   methods of preventing infection of catheters, such as  
intravascular catheters and other body cavity catheters.  
More specifically, but not exclusively, this invention  
relates to infusing a lock solution into an indwelling  
catheter, such as, for example, an indwelling  
20   intravascular catheter, for inhibiting infection in an  
animal having an indwelling catheter.

          By way of background, catheters are used with  
increasing frequency to treat patients requiring a  
variety of medical procedures. The catheters offer many  
25   advantages for patients; for example, catheters provide  
ready access without repeated injections for  
administration of large volumes of fluids, nutrients,  
medications and withdrawal of blood. For example,  
catheters can be used for infusion of fluids such as  
30   drugs, electrolytes or fluids used in chemotherapy, or  
for the removal of blood on an intermittent basis. For  
example, in hyperalimentation treatment, the catheters  
are usually used for infusion of large volumes of fluids.  
In chemotherapy, catheters are used for infusion of drugs

on an intermittent basis, ranging from daily to weekly. For hemodialysis, dual-lumen catheters are typically used--usually three times per week; one lumen allows removal of blood, while the other lumen allows blood to  
5 return.

Catheters can either be acute or temporary for short-term use or chronic for long-term treatment. Catheters are commonly inserted into central veins (such as the vena cava) from peripheral vein sites. Another  
10 alternative is placement of a dual-lumen chronic (tunneled and cuffed) CVDC through the internal jugular vein. Adequate hemodialysis requires removal and return of 250-400 mL of blood per minute. Great care must be taken in the placement and use of a chronic catheter to  
15 prevent infection of the patient at the site of access or within the vascular system.

Chronic venous catheters usually include a DACRON cuff attached to the catheter and placed under the skin, which promotes ingrowth of fibrous tissue, fixes the catheter  
20 in position, and prevents bacterial migration around the catheter. Most chronic central venous dialysis catheters ("CVDCs") in use in the U.S. today have single subcutaneous Dacron® cuffs, placed in the tunnel, 1-4 cm beneath the skin exit site. For dual lumen catheters  
25 such as the Ash Split Cath™ and Bard Hickman® catheters, there is one cuff on the catheter. For single-lumen catheters such as Tesio® catheters, there is a single Dacron cuff for each catheter. For these cuffed, tunneled CVDC there is no apparent or demonstrated  
30 difference in the rate of exit site infection or catheter-related bloodstream infection ("CRBSI"). It is believed that the only chronic CVDC in the U.S. at present that does not have a subcutaneous Dacron cuff is

the Schoen<sup>TM</sup> catheter. In this catheter a subcutaneous plastic clip connects two Tesio catheters. This clip fixes the catheters in position and apparently prevents pericatheter bacterial migration in a manner similar to a  
5 Dacron cuff. Chronic CVDCs are typically made from one of three types of materials: silicone, polyurethane, or polyurethane derivatives.

Catheters, especially chronic venous catheters, have drawbacks. The use of both temporary and chronic CVDC is  
10 associated with certain complications that may require catheter removal, catheter replacement or administration of medical therapies. They can become occluded by a thrombus, and even if extreme care is taken, the catheters can increase a patient's risk of infection.  
15 Intraluminal thrombus formation may impair catheter flow, as can thrombus formation just outside the tip of the catheter. Impairment of the flow may lead to catheter removal or administration of drugs such as tPA to resolve these thromboses.

20 In order to prevent clotting of catheters in blood vessels between uses, the catheters are usually filled with a lock solution that comprises a concentrated solution of the commonly used anticoagulant, heparin (usually up to 10,000 units of heparin per catheter  
25 lumen). The heparin lock solution is injected into each lumen immediately after each use, and typically left in the catheter until the catheter is accessed again. The heparin lock solution is then withdrawn from the catheter before the next use because infusing this amount of  
30 heparin into a patient's bloodstream runs the risk of causing excessive bleeding. During the catheter lock procedure the injected volume of solution is preferably exactly the same as the internal volume of the catheter.

Even when this volume is injected exactly, about 1/3 of the injected anticoagulant volume typically leaves the end of the catheter, causing some anticoagulation of the patient in the hours after a dialysis procedure.

5        In addition, even with the use of a heparin lock solution, the catheter can become occluded between uses from coagulation of blood in the catheter. Blood may be found in the catheter because, for example, an inadequate volume of heparin was infused within the  
10 catheter lumen, the heparin diffused from the lumen, or residual blood remains in the lumen during the catheter lock. This often results in formation of a thrombus with concomitant loss of flow through the lumen. The occluded catheters frequently are removed and/or  
15 replaced.

Furthermore, it has been reported that thrombi and fibrin deposits on catheters may serve as a nidus for microbial colonization of the intravascular devices, and that catheter thrombosis might be one factor  
20 associated with infection of long-term catheters. Thus the use of anticoagulants (e.g., heparin or citrate) or thrombolytic agents may have a role in the prevention of catheter-related bloodstream infections. However, recent in vitro studies suggest that the growth of  
25 coagulase-negative Staphylococci on catheters may also be enhanced in the presence of heparin. In some patients the routine use of heparin to maintain catheter patency, even at doses as low as 250 to 500 units per day, has caused heparin induced  
30 thrombocytopenia (HIT Syndrome) in patients with anti-heparin antibodies. This serious syndrome can result in severe and sudden thromboembolic and hemorrhagic complications.

Heparin solutions have no proven intrinsic antiseptic properties to prevent infection after catheter hub contamination. "Antiseptic", as used herein, means "relating to the prevention of infection by inhibiting the growth of infectious agents", as defined in Stedman's medical dictionary. Heparin, in fact, may help to promote growth of bacteria within the "biofilm" layer of protein on the catheter surfaces (protamine has the opposite effect). The "biofilm" proteins on the catheter surfaces can protect bacteria from antibiotics and white cells. Also, heparin induces the loss of platelets and, paradoxically, can induce clotting in some patients (the "white clot" syndrome). In addition, catheters, particularly venous catheters, are frequently accessed with syringes, or uncapped and directly connected to IV lines, creating a situation wherein the probability of microbial infection is relatively high.

Studies have shown that catheter-related bloodstream infection ("CRBSI") in hemodialysis patients is caused most frequently by Staphylococcus species such as S Epidermidis. However, hemodialysis patients are reported to have a greater proportion of CRBSIs due to S. Aureus than do other patient populations and a significant number of infections are due to gram-negative organisms. The lack of antiseptic properties of a 5000 U/mL heparin lock was confirmed by a study performed by BEC Laboratories, Inc. under the standard USP antimicrobial effectiveness test protocol.

Significant resources are currently being invested in a search for alternatives to heparin for catheter lock that do not have the above disadvantages. One alternative developed by the present inventor is to use concentrated sodium citrate, as described in

International Publication No. WO 00/10385, which is hereby incorporated herein by reference in its entirety. Concentrated citrate is a more effective anticoagulant than heparin, especially in patients with  
5 deficiency of antithrombin-III (such as patients with liver failure). In addition, citrate will not cause peripheral anticoagulation of the patient if some of the injected citrate enters the circulation, since it is rapidly metabolized and distributed. Furthermore,  
10 it was discovered that concentrated citrate had additional advantages when used in a lock solution.

Nevertheless, if a great excess of heparin or citrate is injected into the patient's blood during a catheter lock procedure or by mistaking heparin or citrate as some  
15 other fluid (such as saline) that is injected during the dialysis procedure, then harm can come to the patient. For citrate, rapid injections of large volumes of sodium citrate solution can cause transient symptoms of hypocalcemia, hypotension and arrhythmia. A transient  
20 decrease in calcium level can cause cardiac arrhythmia. Excess heparin can cause excess anticoagulation of the patient's blood and bleeding from a number of sites.

A significant problem is that all of the fluids used in a dialysis unit, including heparin, citrate, saline,  
25 and lidocaine (anesthetic) are all clear. Once a syringe is filled with a fluid, it is difficult or impossible to tell what is the fluid within the syringe absent careful marking of the syringe. Though attempts are made to label syringes after filling them when they are pre-filled, it  
30 is up to the user to remember what fluids they have just drawn into syringes.

As further background, another complication associated with chronic CVDC is infection. As noted

above, when catheters are inserted into veins or arteries, they bypass the protective dermis layer, and provide direct access to a patient's blood stream. The same applies for insertion of a catheter into another  
5 body cavity. This can cause the inadvertent transfer of infectious agents into the vein or artery at the location of the catheter.

Hemodialysis catheters may become contaminated by a variety of mechanisms. During placement of the  
10 catheter and early use if there is bacterial contamination of the catheter, bloodstream infection is seen several days to weeks later. Later in the use of catheters other factors determine the risk of infection, including, for example, the following: (a)  
15 penetration of organisms around the catheter from the skin following exit site infection; (b) contamination of catheter connections during attachment of dialysis tubing or syringes; (c) contamination of blood as it passes through the dialysis system, (d) administration  
20 of contaminated blood or other solutions through the catheter during or after the dialysis session or, (e) endogenous bloodstream infection during or between dialysis treatments.

For the above reasons, catheters have a propensity to  
25 become contaminated. Bloodstream infection and localized infections of the skin exit site are common in hemodialysis patients. If there is bacteremia (bacteria in blood), then the catheter surfaces within the vein or artery can become seeded with bacteria. In either case,  
30 the patient can develop septicemia (infection in the blood) and become seriously ill.

For chronic CVDC the most common cause of catheter infection is contamination of the connector hub. The



predominant route of contamination is endoluminal. The major determinant of the rate of infection is the frequency with which the catheter hub is opened and the major preventive step is the care in disinfection of the hub and prevention of contamination of the hub. Since endoluminal contamination is the major cause of CRBSI in chronic CVDC, the determinants of infection center on the procedures and handling of the catheter.

In addition, the foreign surfaces of catheters can create a smooth surface at which bacteria can grow, and at which the white cells are unable to surround or "phagocytize" the bacteria. Several studies have indicated a rate of bloodstream infection during use of chronic CVDC of 1.1 per 1,000 patient days to 2.2 per 1,000 patient days. One study demonstrated a catheter-related bacteremia rate of 2.2 to 3.8 bacteremic episodes per 1,000 patient days, the lower rate being for catheters placed surgically rather than radiologically. Another study of new tunneled catheters reported that 19% of catheters became infected in a mean of 62 days after catheter placement, representing a rate of 3 infections per 1,000 days. This means that each patient has approximately a 10% chance of developing bloodstream infection during each month. There is no evidence that the rate of CRBSI increases with duration of use of a chronic CVDC. In fact, practical experience and various studies have shown that the rate of CRBSI is the same over the many months of use. Tests indicate that the risk of CRBSI is the same for each period of time that the patient has a catheter. Over time the patient has a higher chance for infection merely because there is more time at risk for infection. The longer the patients have chronic CVDC, the greater the chance that an infection

will occur, but this is merely due to greater time for a constant risk of exposure.

CRBSI in dialysis patients is usually associated with modest symptoms and clears after antibiotic therapy.

5 However, in some patients, signs of infection are much more severe and include all of the symptoms of Systemic Inflammatory Response Syndrome ("SIRS") (tachycardia, tachypnea, abnormal temperature and white count) plus hypotension. Often these patients must be hospitalized  
10 and given intravenous antibiotics. In spite of this care, patients often remain seriously ill until the infected catheter is removed.

Similarly SIRS can occur in ICU patients with CRBSI due to central venous catheters. The mortality rate  
15 following CRBSI in ICU patients has been reported to be 3-25%. Of the 300,000 patients on dialysis in the U.S., about 60,000 have chronic CVDC. Assuming an average incidence of CRBSI of only 21,000 patient-days at risk, about 120 of these patients develop CRBSI each day. At  
20 the lowest reported mortality rate of 3%, 3-4 ESRD patients die from CRBSI each day. At the highest reported mortality of 25%, 30 ESRD patients die from CRBSI each day. The cost attributable to caring for a single CRBSI episode in hospitalized patients has been  
25 reported to be between \$3,700 and \$29,000. Costs may be similar for patients with CRBSI related to chronic CVDC, given the higher cost of removing and replacing a chronic CVDC. Given the serious consequences of CRBSI, the acute illness of the patient who apparently has bacteremia, and  
30 the frequent decision to remove the catheter on the presumption that it is the source, there is a great need for alternative means for fighting catheter infection.

Furthermore, because of frequent hospitalizations and receipt of antibiotics to treat bloodstream and vascular access infections, hemodialysis patients are at high risk for infection with drug-resistant bacteria. Studies have  
5 shown that among vascular access types, arteriovenous fistulas created from the patient's own blood vessels have the lowest rates of infection; grafts constructed from synthetic materials have intermediate risk; and central catheters have the highest risk. The rapid increase in  
10 vancomycin-resistant enterococci (VRE) in the United States has been attributed to use of antimicrobials, especially empirically prescribed vancomycin. Vancomycin is used commonly in dialysis patients for empiric therapy of symptoms of bloodstream infection because it can be  
15 administered once a week and is effective against two common pathogens, coagulase-negative Staphylococci and Staphylococcus Aureus. The greater the use of vancomycin, however, the greater the risk of inducing vancomycin-resistant staphylococcus, and if this is the cause of  
20 septicemia, there are then no effective drugs with which to treat these patients. Use of prophylactic vancomycin and other antibiotics to prevent catheter infection is therefore discouraged, and alternate means for fighting catheter infection are greatly needed.

25 Catheters are also used to convey fluids into and out of other body cavities besides veins, as noted above. Catheters are placed into arteries to measure blood pressure or remove arterial blood for analysis of gases reflecting lung function. Catheters are placed into the  
30 peritoneum (the space surrounded by the peritoneal membrane and external to organs in the abdomen) to perform peritoneal dialysis and remove fluids and toxins from the patient. Other catheters are placed into the

fluid around the nervous system (cerebral spinal fluid)  
for removal of this fluid or administration of drugs, and  
into the subcutaneous space for administration of various  
drugs or fluids. Such catheters are also subject to  
5 infection and to other problems addressed herein.

Thus in light of the above described problems, there  
is a continuing need for advancements in the field of  
catheter lock solutions. The present invention is such  
an advancement and provides a wide variety of benefits  
10 and advantages.

### SUMMARY OF THE INVENTION

In one form, the present invention provides a catheter lock solution that includes an anticoagulant and a photo-oxidant. In one embodiment the  
5 anticoagulant is heparin, and in another embodiment the anticoagulant is citrate. In one embodiment, the photo-oxidant is methylene blue, and in other embodiments other photo-oxidants are used. The solution in other embodiments also includes a  
10 viscosifying agent and/or additional pharmaceutically acceptable materials. In certain embodiments, the pH is controlled to enhance the safety and the effectiveness of the solution. The relative density of the solution is also selected in certain embodiments to  
15 optimize the length of time that the solution remains in a catheter.

In another form, the present invention relates to catheter lock solutions that include compositions with intrinsic color (hereafter a "coloring agent"). A  
20 coloring agent can be included in an inventive catheter lock solution to make the solution immediately recognizable in a syringe or in a catheter lumen (avoiding accidental infusion to the patient). The colored solutions may advantageously be combined with  
25 citrate, heparin, or other anticoagulants that can prevent coagulation within the catheter and may also be used in conjunction with alternative antibacterial and/or antifungal compositions.

In yet another form, the present invention  
30 provides methods for treating patients having an indwelling intravascular catheter. In one embodiment, the method comprises selecting a patient having an indwelling intravascular catheter defining a lumen

therethrough; and infusing an inventive catheter lock solution into the lumen. The invention is particularly useful in treating a patient having an infection or a substantial risk of infection related to the presence  
5 of the catheter. When a solution including methylene blue is used, the method can also include exposing the solution to light or other radiant energy to enhance the antiseptic properties of the solution.

In still another form, the invention provides  
10 devices, methods and compositions relating to the pretreatment of a catheter or other medical implant prior to use. In one embodiment, the catheter is soaked in a methylene blue solution for a period of time, and thereby impregnated with methylene blue to  
15 provide a catheter featuring resistance to infection.

In still another form, the present invention provides a kit for accessing a patient's intravascular system. The kit includes a container having therein an inventive catheter lock solution; a syringe with Luer  
20 lock tip; a replacement cap; and a needleless single-dose vial access spike with dead cap.

Further objects, features, aspects, forms, advantages and benefits shall become apparent from the description and drawings contained herein.

25 While the actual nature of the invention covered herein can only be determined with reference to the claims appended hereto, certain forms and features, which are characteristic of the preferred embodiments disclosed herein, are described briefly as follows.

**BRIEF DESCRIPTION OF THE DRAWINGS**

Figure 1 is a perspective view of one embodiment of a catheter and syringe for infusing a lock solution into a catheter for use with the present invention.

Figure 2 is a graph depicting the effect of methylene blue (12 mg/100ml) on concentration of a gram negative organism, *Escherichia Coli*, without light exposure. All *E. Coli* are killed within one day.

Figure 3 is a representation of the effect of methylene blue (12 mg/100ml) on concentration of a gram positive organism, *Enterobacter Faecalis*, without light exposure. All *Enterobacter* are killed within one day.

Figure 4 is a representation of antibacterial properties of methylene blue 0.01% in ACD (4% citrate) for gram positive organisms and gram negative organisms.

Figure 5 is a representation of antiseptic properties of methylene blue 0.01% in 0.24 Molar citrate buffer at pH 4.5 and 7.2 for gram-positive organisms and gram-negative organisms.

Figure 6 depicts a linear graph showing the relationship of densities of various catheter lock solutions to citrate concentration.

25

DETAILED DESCRIPTION OF THE INVENTION

For the purposes of promoting an understanding of the principles of the invention, reference will now be made to the embodiments illustrated herein and specific language will be used to describe the same. It will nevertheless be understood that no limitation of the scope of the invention is thereby intended. Any alterations and further modifications in the described processes, systems or devices, and any further applications of the principles of the invention as described herein, are contemplated as would normally occur to one skilled in the art to which the invention relates.

In accordance with the invention a catheter lock solution is used to provide anticoagulant and antibacterial properties to an implanted catheter as the lock solution resides in the catheter between uses. As used herein, the term "lock solution" refers to a solution that is injected or otherwise infused into a lumen of a catheter with the intention of allowing at least a portion of a lock solution to remain in the lumen until it is desired or required to access that particular lumen again, typically for additional treatment, i.e., infusion or withdrawal of fluid. It is desired that at least a portion the lock solution remain in the lumen for a desired amount of time lasting from about 1 hour to 3 or 4 days or longer. However, frequently the lock solution is changed on a daily basis during regular care and sterile maintenance of the indwelling catheter. Use of a lock solution in accordance with the present invention provides particular advantages for patients with catheters by inhibiting catheter-related infections and by preventing catheter occlusion.



Catheters used in connection with the present invention typically can either be acute (temporary) or chronic (long-term) catheters surgically implanted in the animal. The catheters usually are inserted into a vein or artery. The catheters are typically used in varying intervals to administer fluids, nutrients, and medications into the body. The catheters also can be used to withdraw body fluids, such as blood, for hemodialysis treatment. When not in use, the catheter remains in its position, commonly an intravascular position, until a subsequent treatment is performed.

The catheters that may be used accordance with this invention include known and commonly used catheters and are readily available from a variety of commercial sources. The catheters may vary in configuration and size. One type of catheter commonly used in accordance with this invention is a tunneled catheter that includes a cuff for ingrowth of tissue to anchor the catheter. Examples of catheters that may be used include, but are not restricted to, an ASH SPLIT CATH and DUOSPLIT by Ash Medical Systems (West Lafayette, Indiana) and Medcomp (Harleysville, Pennsylvania); Tesio Catheters by Medcomp; PERM CATH by Quinton Instrument Company (Seattle, Washington); and HICKMAN and VAS CATH by Bard, Inc. (Salt Lake City, Utah). Catheters containing totally subcutaneous ports are also useful in the present invention; examples include LIFESITE by Vasca (Topsfield, Maine); and DIALOCK by Biolink, Inc. of (Boston, Massachusetts).

Figure 1 depicts one example of a catheter for use with this invention. Catheter 10 is a dual lumen catheter and includes an outer sheath 12 having a cuff 38 and first and second lumens 14 and 16, respectively.

Lumens 14 and 16 extend from distal tip 18 through sheath 12 and exit from sheath 12 at connection 36. Each of lumens 14 and 16 include releasable clamps 20 and 22, respectively. Each of lumens 14 and 16  
5 terminate in a threaded end 24 and 26, which can be threadedly attached to protective end caps 28 and 30, respectively. Fluids including a lock solution can be infused or withdrawn from each lumen 14 and 16 by inserting needle 32 of a syringe 34 through protective  
10 end caps 28 and/or 30 after protective end caps 28 and/or 30 have been sterilized by cleaning successively, for example with Betadine and alcohol. Alternatively, one or both protective end caps 28 and 30 can be removed and threaded ends 24 and 26 can be  
15 threadedly attached via a connector (not shown) to lines for infusion or withdrawal of fluids (not shown). Once a desired treatment session has been completed, the needles are removed or the connectors are replaced with fresh, sterile protective end caps. The lumens  
20 are then typically flushed with normal saline, after which a lock solution is injected into each lumen. All procedures are performed using standard sterile techniques well known to those skilled in the art. The catheters for use with this invention can be prepared  
25 from a variety of materials, including, for example, silicon, polyurethane, polyvinyl, silicone, or silastic elastomer.

Chronic catheters are usually inserted through an internal jugular vein into the superior vena cava.  
30 Usually these catheters include a cuff attached to the exterior of the catheter and placed under the skin, which promotes ingrowth of fibrous tissue, and thus fixes the catheter in position and prevents bacterial migration

around the catheter. The catheters are manufactured to function for several months. For example, TESIO catheters can last for up to four years with proper intervention. However, in actual practice prior to the  
5 present invention, the catheters have exhibited limited longevity because of occlusion and/or infection. The catheters frequently must be removed and/or replaced upon the occurrence of occlusion and/or infection.

In one form, the present invention provides a  
10 catheter lock solution including an anticoagulant and a photo-oxidant. In certain embodiments, a photo-oxidant is selected that has an antiseptic effect in the lock solution. As used herein, the term "photo-oxidant" is intended to refer to a compound (usually an organic dye)  
15 that has photo-oxidation properties, in which the compound exhibits an increased oxidizing potential upon exposure to radiant energy such as light. The term "photo-oxidant" also refers to a composition that releases one or more electrons when struck by light. In  
20 various embodiments, the lock solution aids in the prevention of infection and occlusion of an indwelling catheter.

It is understood that the photo-oxidant should be safe for use in a catheter surgically positioned within a  
25 patient's body, such as, for example, an intravenous catheter. The photo-oxidant must also be compatible with an anticoagulant selected for use in the catheter lock solution, when present. In one preferred aspect of the invention, the photo-oxidant is methylene blue, which  
30 advantageously provides antibiotic and antifungal activity, and also provides particular advantages by reducing incidence of catheter occlusion, and providing a color to make the catheter lock solution clearly

identifiable within a syringe or a catheter. In addition to methylene blue, other photo-oxidants may be used to alternatively provide antibiotic and antifungal activity, to provide particular advantages by reducing incidence of catheter occlusion, and/or to provide a color to make the catheter lock solution clearly identifiable within a syringe or a catheter. For example, it is expected that alternative photo-oxidants that can be used to achieve one or more advantageous result of the invention include Rose Bengal, hypericin, methylene violet, proflavine, rivanol, acriflavine, toluidine blue, trypan blue, neutral red, a variety of other dyes or mixtures thereof. Therefore, in alternate aspects of the invention, one or more alternative photo-oxidants, preferably a colored photo-oxidant is used in accordance with the invention in place of methylene blue.

It has unexpectedly been determined that methylene blue has surprisingly effective antibacterial activity when used in accordance with the present invention, especially when exposed to light. In a series of tests, with a gram negative and a gram positive organism, methylene blue inactivated all bacteria within 1 day, while heparin and a 4% concentration of citrate caused no effect on gram positive organisms (Figures 2,3). Methylene blue also advantageously colors the lock solution blue, which provides a useful tool to medical personnel in preventing confusion between the lock solution and any other solution that might be present in a syringe or the catheter.

In vitro, methylene blue has marked bactericidal properties at relatively low concentrations. These properties do not require the presence of light, but it

is expected that the bactericidal properties would be enhanced by exposure to light.

Methylene blue at a concentration of 0.01% (10 mg/100 mL) has been shown to kill gram-negative organisms within one day. In addition, methylene blue and 4% citrate at pH 4.5 (in the form of Anticoagulant Citrate Dextrose ("ACD") solution) kills gram positives such as enterococcus within one day. Figure 4 sets forth data showing the antibacterial properties of methylene blue 0.01% in ACD (4% citrate) for gram positive organisms and gram negative organisms. The data depicted in Figure 4 is also set forth below in Table I:

15

**Table I**

<b>Organism</b>	<b>Day 0</b>	<b>Day 0.0416</b>	<b>Day 1</b>	<b>Day 7</b>
<u>P. aeruginosa</u>	2.41E+06	4.1E+03	1.00E+00	1.00E+00
<u>E. coli</u>	3.00E+04	1.52E+04	1.00E+00	1.00E+00
<i>S. aureus</i>	1.36E+06	5.22E+05	1.60E+03	1.00E+00
<i>E. faecalis</i>	3.11E+06	1.11E+06	2.365E+04	1.00E+00

Although it is not intended that the present invention be limited by any theory by which it achieves its advantageous result, it is believed that the mechanism of antiseptic properties of methylene blue is through its oxidation potential. Due to the interactions of hydrogen ion with redox potential, methylene blue is expected to be more effective at a neutral pH than acidic pH.

In one form of the invention, therefore, a lock solution is provided that comprises methylene blue in a concentration effective to kill bacteria. In one embodiment, the lock solution has a methylene blue concentration of up to about 1500 mg/100 ml, preferably from about 1 mg/100 ml to about 1500 mg/100 ml. In

another embodiment, the lock solution has a methylene blue concentration of from about 1 to about 1000 mg/100ml. In another embodiment, the lock solution has a methylene blue concentration of from about 1 to about 100 mg/100ml. In  
5 yet another embodiment, the lock solution has a methylene blue concentration of from about 1 to about 50 mg/100 ml. In still another embodiment, the methylene blue concentration is about 10 mg/100 ml.

Another excellent property of methylene blue when  
10 selected for use in accordance with the invention is its color, and a determination of a concentration for a given solution can be based in part upon the intensity of color that develops. The color has a safety function, indicating to observers that the catheter contains a  
15 catheter lock solution. At 10 mg/100ml, the preparation has a dark blue color in a syringe, and a noticeably blue color within the clear external segments of the catheter. Over time, the methylene blue solution lightly stains the inside of external segments made of polyurethane or  
20 silicone, but the injected lock solution still makes the segments noticeably darker in color. Therefore the presence of the lock solution is recognizable.

As stated above, a catheter lock solution in certain embodiments of the present invention also includes an  
25 anticoagulant. Examples of anticoagulants include, for example, heparin and citrate. When the anticoagulant includes heparin, the heparin is preferably present at a concentration of from about 100 units/ml to about 10,000 units/ml.

30 In certain preferred aspects of the invention, the anticoagulant is citrate. Citrate is preferably present at a molar concentration at least as high as the molar calcium concentration in a patient's blood. In one

preferred embodiment, citrate is present in a lock solution at a concentration of from about 1.5 to about 47 percent by weight. In another embodiment, citrate is present at a concentration of from about 1.5 to about 23 percent by weight. In yet another embodiment, citrate is present at a concentration of from about 1.5 to about 15 percent by weight. In another embodiment, citrate is present at a concentration of about 7 percent by weight. In still another embodiment, citrate is present at a concentration of at least about 0.004 Molar, more preferably from about 0.01 to about 1.0 Molar. Another embodiment includes citrate at a concentration of from about 0.1 to about 0.5 Molar. Yet another embodiment includes citrate at a concentration of about 0.24 Molar.

Although it is not intended that the present invention be limited by any theory whereby it achieves its advantageous results, in a lock solution including citrate, it is believed that the citrate prevents coagulation by chelating the calcium in the adjacent blood. Thus, in one preferred embodiment, the solution contains sufficient citrate ions to effectively chelate at least an amount of calcium that would be present in a quantity of blood equivalent to the volume of a catheter lumen. In other preferred embodiments, the solution has a significantly higher citrate ion concentration. In general, the arterial and venous lumens of tunneled central venous catheters typically have an internal volume in the range of 1.5-2.5 ml. A 0.24 M citrate solution contains 0.24 mmol/mL of citrate ion which is approximately 50 times the citrate required to chelate the calcium in the volume of blood found in a catheter lumen.

In addition, it has been found that concentrated citrate has antibacterial and antifungal properties. As

stated above, information relating to the use of concentrated citrate is included in International Publication No. WO 00/10385, which is incorporated by reference herein. The ability of citrate to kill

5 microorganisms has been shown to increase with an increase in the concentration of citrate. When citrate is mixed with large numbers of gram negative bacteria, all are killed within 1-7 days. Depending upon pH and concentration, large numbers of gram positive organisms

10 are killed between 7 and 21 days. Fungi may also be killed by contact with citrate; however, fungi take longer to kill. It is believed that citrate's ability to kill bacteria and fungi is higher for the few numbers of organisms that contaminate the connector of a catheter

15 during dialysis. Where a citrate concentration is selected that does not have a suitable rate of killing microorganisms, the lock solution will preferably include another antibacterial component for enhancing the antiseptic effect of the solution.

20 In one preferred embodiment, an inventive catheter lock solution includes 0.24 Molar citrate (provided, for example, in the form of trisodium citrate dihydrate) and methylene blue at a concentration of 10 mg/100 ml. When this solution is infused into a

25 catheter, the methylene blue slowly penetrates through the biofilm to stain the inside of the catheter. A lock solution having this concentration of methylene blue creates a light stain of the external clamping segments of a chronic CVDC, which allows an observer to

30 still visualize the interior to see whether it contains the lock solution, saline, or blood. As methylene blue slowly penetrates through the biofilm to stain the inside of the catheter, it is believed that citrate



also penetrates through the biofilm. The presence of methylene blue and/or citrate within the biofilm and in the surface of the catheter are also believed to prevent bacterial growth in these locations.

5 In another embodiment of the invention, a citrate/methylene blue lock solution is provided having a pH of from about 4 to about 8. In another embodiment, the solution has a pH of from about 4.5 to about 8. In still another embodiment, the solution has a pH of from about 6  
10 to about 8. In yet another embodiment, the pH is from about 6.7 to about 7.7. Another embodiment features a pH of from about 7.0 to about 7.4. In one preferred embodiment, the pH is about 7.2. Based upon in vitro testing, and the known relationship between pH and  
15 oxidation potential, it is believed that antimicrobial effects of methylene blue are greater at approximately neutral pH than at acidic pH. For example, citrate at 7% concentration in the presence of methylene blue at a concentration of 10 mg/100 ml has been found to be more  
20 effective at approximately neutral pH than at 4.5 pH. Specifically, an inventive citrate/methylene blue catheter lock solution including 0.24 Molar citrate (as trisodium citrate dihydrate) and 10 mg/100 ml methylene blue at pH  $7.2 \pm 0.1$  pH units and with a relative density  
25 of from about 1.035 to about 1.045 at 20°C has been tested to determine the antibacterial properties, against both gram-negative and gram-positive organisms. The results, which are set forth in Figure 5, indicate highly effective antibacterial properties. The data represented  
30 in Figure 5 are also set forth below in Table II:

Table II

DAY	<i>E. coli</i>		<i>P. aeruginosa</i>		<i>S. aureus</i>		<i>E. faecalis</i>	
	pH 7.2	pH 4.5	pH 7.2	PH 4.5	pH 7.2	PH 4.5	pH 7.2	pH 4.5
0	8.15E+06	8.15E+06	1.45E+06	1.45E+0.6	2.36E+06	2.36E+06	2.1E+06	2.1E+06
1	1.00E+00	6.5E+03	1.00E+00	1.00E+00	1.00E+00	1.00E+00	1.00E+00	2.34E+05
2	1.00E+00	1.00E+00	1.00E+00	1.00E+00	1.00E+00	1.00E+00	1.00E+00	3.9E+03
3	1.00E+00	1.00E+00	1.00E+00	1.00E+00	1.00E+00	1.00E+00	1.00E+00	1.00E+00

5

A problem with all catheter lock solutions is that they do not permanently stay within the catheter. Some of the catheter lock solution exits the end of the catheter during the infusion (often about 1/3 of the injected volume). In addition, the portion remaining in the end of the catheter is typically washed out slowly by flow of blood through the side-holes of the catheter (if present). Other lock solution slowly diffuses from the body of the catheter through the end of the catheter during the time that lapses between dialysis treatments.

In the case of concentrated citrate, for example, gravitational effects also come into play. It is of course understood that the densities of citrate solutions increase as the concentrations of citrate therein increase. The relative density of 23% citrate, for example, is 1.120, which is significantly higher than the relative density of blood. Thus, when the patient is erect, the segment of the inner portion of the catheter in the vena cava is vertical. Gravitational force causes citrate at this concentration to slowly leave the catheter. In the laboratory, in some types of catheters positioned vertically (such as the double-D shaped Ash Split Cath catheters), 23% citrate lock can be shown to slowly exit from the distal part of the catheter over 3-5 days, into blood or blood substitute (with the same relative density). In other catheters (such as

cylindrical Tesio catheters) the 23% citrate lock does not exit over time.

From bacteriologic studies and initial clinical trial results, it is believed that the optimal concentration of citrate in a catheter lock solution in the absence of other components having significant antibacterial effect is at least 10% concentration, with a pH of 4.5. However, for this concentration of citrate to be effective, it should remain within the catheter lumen between dialysis treatments. In vitro studies have indicated that the density of the lock solution is critically important in determining the length of time that the lock solution remains in the catheter. The relative density of blood with hematocrit of 32% is approximately 1.045. If a catheter lock solution with relative density higher than this is placed into a catheter positioned vertically, the lock solution will exit from the catheter at a slow rate. Increasing the viscosity with polymeric substances such as PEG slows but does not prevent the egress of the lock solution. Therefore, in certain embodiments of the invention, the citrate concentration in a lock solution is selected such that the density of the lock solution is sufficiently close to the density of the patient's blood that the solution does not exit the catheter during the lock period to an unacceptable degree. It is believed that 0.24 Molar citrate alone does not have significant antibacterial effect at neutral or acid pH; however, the antithrombotic effect of 0.24 Molar citrate will remain very high even with some diffusion out of the catheter, and the antibacterial function in the lock solution can

be supplemented in accordance with the invention, for example, by including methylene blue in the solution.

In one aspect of the invention, therefore, a catheter lock solution is provided that has a density of from about 1.000 to about 1.300 g/ml. In another embodiment, a lock solution is provided having a density of from about 1.000 to about 1.080 g/ml. In still another embodiment, a lock solution is provided having a density of from about 1.030 to about 1.050 g/ml. In yet another embodiment, an inventive lock solution has a density of from about 1.035 to about 1.045 g/ml. It is understood that the density of a given patient's blood may differ from the density of the blood of another patient; however, matching the relative density of the catheter lock solution to the relative density of whole blood of a patient is well within the purview of a person of ordinary skill in the art. Closely matching the densities has the advantageous effect of aiding in the retention of the catheter lock solution within the catheter between treatments. When the relative densities are relatively close, gravitational force does not tend to urge the catheter lock solution out of the catheter when the patient is upright. Similarly blood will not enter the catheter when the catheter is upward directed as in the femoral vein and the patient is standing (as can happen with a low-density catheter lock such as heparin).

The densities of various formulations of various catheter lock solutions are directly related to the citrate concentration, as reflected in the linear graph set forth in Figure 6. In a preferred embodiment, the density of the lock solution is less than blood with a hemocrit of 32 (i.e., from about 1.035 to about 1.045). As such, in one embodiment, the lock solution has a citrate concentration of up to about 0.24M (i.e., up to about 7% by weight). A

solution having a citrate concentration of 0.24M has a relative density of about 1.045. This concentration of citrate does not have strong antiseptic properties, but is still highly effective as an anticoagulant even if diluted  
5 by blood at the tip of the catheter. The antiseptic function can be supplemented in accordance with the invention by including methylene blue in the lock solution with the citrate. Indeed, a citrate concentration of about 7% provides anticoagulant properties superior to  
10 concentrated heparin. A higher concentration of citrate would be desirable for antiseptic and anticoagulant effect; however, in order to retain a significant proportion of the citrate within the catheter body, a density that is more closely aligned with blood density is preferred.

15 In another aspect of the invention, the catheter lock solution may also include an agent to increase viscosity, as described in International Publication No. WO 00/10385, which is incorporated herein by reference in its entirety. The presence of a viscosifying agent is  
20 particularly useful, for example, when the relative density of a given catheter lock solution is not the same as the density of a patient's blood.

Therefore, in certain preferred embodiments, a lock solution is provided that comprises a photo-oxidant, an  
25 anticoagulant and one or more agents to adjust viscosity to help retain the lock within the catheter for a desired amount of time. It is well known that catheters are manufactured to have a variety of configurations and lumen diameters. For example, catheters can include  
30 single or double lumens. The double lumens can be fused adjacent to each other or they can be concentric. The lumens can have varying cross-sectional areas and shapes, ranging from substantially circular to substantially

ovoid. As discussed above, a phenomenon common to most lock solutions is that a portion of the solution at the distal end of the lumen diffuses into the patient's blood stream and is replaced in the catheter by blood. The  
5 rate of diffusion of a lock solution from a lumen can be influenced not only by the density of the lock solution, but also by the cross-sectional shape and area of the particular lumen(s) and the viscosity of the lock solution. A lock solution of the present invention is  
10 preferably prepared to have a viscosity and density such that a substantial portion of the lock solution does not diffuse or flow out of a catheter lumen within several days.

Viscosifying agents that can advantageously be  
15 selected for use in accordance with the present invention include those pharmaceutically acceptable agents known or commonly used in treatment of animals including humans. Examples include, but are not limited to, dextran, polyethylene glycol, glycerin, polygeline, and non-  
20 metabolizable sugars such as sorbitol and mannitol and mixtures of these compounds. An excellent aspect of the invention, therefore is a composition useful as a lock solution that comprises methylene blue (or other photo-oxidant), a citrate salt (or other anticoagulant) and a  
25 viscosifying agent. The viscosifying agent allows a higher concentration of citrate to be used without having an unacceptable degree of egress of the lock solution from the catheter due to high density of the lock solution.

30 While it is understood that optimal viscosity and density are dependent upon the shape and size of a particular lumen, a person of ordinary skill in the art, in view of the description herein, can readily determine

a desired density and viscosity for a particular catheter without undue experimentation. It is of course understood that the need for viscosifying agents is reduced in a lock solution having a relatively lower concentration of citrate and a density closely matched to that of blood. The antiseptic effect of the citrate, which is reduced by the reduction in the citrate concentration, is replaced by the inclusion of methylene blue or other photo-oxidant in an amount that provides an antiseptic effect.

An inventive lock solution can be prepared to include a variety of other pharmaceutically acceptable agents. For example, the lock solution can include salts, such as, for example, sodium chloride or other sodium salts. The lock solution can also include a variety of other antibacterial, antimicrobial and anticoagulant agents. Such antibacterial and antimicrobial agents are well known to those skilled in the art and can include, without limitation, gentamicin, vancomycin, and mixtures of these agents. Additional anticoagulant agents include, for example, urokinase, tissue plasminogen activation (tPA) and mixtures of these agents.

By "pharmaceutically acceptable", it is meant that the lock solution and the included salts and other additives which are, within the scope of sound medical judgment, suitable for use in contact with tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, and are commensurate with the reasonable benefit/risk ratio. It is also typically necessary that a composition be sterilized to reduce the risk of infection. For example, pharmaceutically acceptable salts are well-known in the art, for example, as found in S.M. Berge

et al. described in detail in J. Pharmaceutical Science, 66:1-19, 1977.

The present invention also provides methods of inhibiting infections in animals having an indwelling intravascular catheter. In one embodiment, a lock solution including a photo-oxidant is provided, the solution in certain embodiments also including an anticoagulant, and the lock solution is then infused into the lumen or a catheter to lock the catheter.

Once a lock solution is infused into the lumen of a catheter in accordance with the invention, it is preferably allowed to remain until that particular catheter or lumen is desired to be accessed again. Especially with heparin, it is important to remove the catheter lock before starting the dialysis procedure, or using the catheter for fluid infusion.

A great advantage of methylene blue or other colored photo-oxidant selected in accordance with the invention, as discussed above, is that it provides color to the lock solution. This color indicates to health professionals using the catheter that it is filled with a catheter lock solution. Indeed, in accordance with another aspect of the invention, different colorants are included in various solutions used in connection with catheters and/or syringes in a given system so that medical personnel will be able to ascertain what type of solution is in the catheter or syringe by simply observing the color of the solution. In this regard, a plurality of photo-oxidant compositions in accordance with the invention may be used in a color-coding system.

In another excellent aspect of the invention, a lock solution including methylene blue or other photo-oxidant is exposed to light either before or after



infusion into an indwelling catheter. While it is not intended that the invention be limited by any theory whereby it achieves its advantageous result, it is believed that the antibacterial effect of the methylene blue and other photo-oxidants is enhanced by exposure to light. The exposure can be achieved, for example, by exposing the solution to ambient light prior to infusion into the catheter, by exposing the solution to high intensity light prior to infusion into the catheter, or by exposing the solution to one or more pulses of light after it is infused into the catheter. The present invention also contemplates the placement of a light source on or near an indwelling catheter at various locations to provide a manner in which to expose a lock solution to light as it resides in the catheter.

In another embodiment, the catheter lock solution containing methylene blue or other photo-oxidant may be injected into catheters used for access to other body spaces besides veins or arteries. For example, catheters used in peritoneal dialysis access the peritoneum (the space defined by the peritoneal membrane and exterior to the organs in the abdomen). These catheters also have a risk of bacterial and fungal contamination. After draining and infusing peritoneal dialysate solutions, a lock solution including methylene blue or other photo-oxidant is infused into the catheter. Other catheters with risk of infection include catheters in the urinary bladder, the cerebral spinal fluid (around the central nervous system) and the subcutaneous space (under the skin).

The present invention also contemplates the pretreatment of a catheter to provide an infection-

resistant catheter. In an advantageous aspect of the invention, therefore, a catheter selected for implantation into a patient, such as, for example, into a vascular site of a patient, can be pretreated with a methylene blue solution to coat and impregnate the catheter surfaces with methylene blue, thereby providing an infection-resistant catheter. Generally, it is sufficient to soak the catheter in an excess volume of an aqueous methylene blue solution, followed by washing in water or in a solution mimicking physiological conditions of use to remove non-absorbed material. The catheter, pretreated in this manner, can then be placed into position having an increased resistance to infection.

It is also contemplated that a wide variety of other polymeric medical devices can be treated as described above. For example, medical devices that are amenable to coating and impregnation by methylene blue include non-metallic materials such as thermoplastic or polymeric materials. Examples of such materials are rubber, plastic, polyethylene, polyurethane, silicone, Gortex (polytetrafluoroethylene), Dacron (polyethylene tetraphthalate), Teflon (polytetrafluoroethylene), latex, elastomers and Dacron sealed with gelatin, collagen or albumin. Devices especially suited for application of the antimicrobial combinations of this invention include, for example, peripherally insertable central venous catheters, dialysis catheters, long term tunneled central venous catheters, peripheral venous catheters, short-term central venous catheters, arterial catheters, pulmonary artery Swan-Ganz catheters, urinary catheters, long term urinary devices, tissue bonding urinary devices, vascular grafts, vascular catheter ports, wound drain tubes,

hydrocephalus shunts, peritoneal catheters, pacemaker capsules, small or temporary joint replacements, urinary dilators, heart valves and the like.

One embodiment of the present invention,  
5 therefore, is a method for impregnating a non-metallic medical implant with methylene blue comprising the steps of forming an aqueous methylene blue solution of an effective concentration to inhibit the growth of bacterial and fungal organisms; and applying the  
10 solution to at least a portion of a medical implant under conditions where the methylene blue permeates the material of the medical implant. The solution of methylene blue can have a wide variety of concentrations, depending upon the amount of methylene  
15 blue one desires to become impregnated in the catheter or other device. In addition, the amount of time that the catheter or other device is soaked in the methylene blue solution can be varied to vary the degree of impregnation. Typically it will be desired to soak the  
20 catheter for at least about an hour, and often significantly longer.

After the impregnated implant is removed from the solution, and optionally allowed to dry, the implant is preferably rinsed with a liquid to remove excess  
25 methylene blue from the surface thereof. It is of course understood that the invention can be used in certain embodiments to pretreat a portion of a catheter or other device. In the case of an intravascular catheter, for example, it may be desirable to pretreat  
30 only the lumen of the catheter. This can be done by simply placing a pretreatment solution into the lumen of the catheter rather than soaking the entire catheter. Alternatively, it is possible to pretreat

only a portion of a catheter that will reside within a patient's artery or vein, or to pretreat only the portion that lies transcutaneously.

In another aspect of the invention, there is provided a catheter lock kit. In one preferred embodiment, a kit includes four sterile components as follows: (1) 5cc of catheter lock solution (such as the solution described in Example 3); (2) a 3cc syringe with Luer lock tip; (3) a replacement cap; and (4) a needleless single-dose vial access spike with dead cap. The catheter lock solution can be advantageously provided in the form of a 5 mL vial that has been aseptically filled with the solution. A suitable sterile single use hypodermic syringe is commercially available from Becton Dickinson, One Becton Drive, Franklin Lakes, NJ. A suitable catheter lumen replacement cap is commercially available from B. Braun Medical, Inc., 824 12<sup>th</sup> Avenue, Bethlehem, PA. A suitable single dose vial access spike is commercially available from ICU Medical, Inc., 951 Calle Amanecer, San Clemente, CA.

As can be appreciated by those of skill in the art, in one embodiment there has been described an aqueous catheter lock fluid comprising an anticoagulant and a photo-oxidant, wherein the fluid has a density of from about 1.000 to about 1.300 g/ml. In certain embodiments, the photo-oxidant comprises a member selected from the group consisting of methylene blue, Rose Bengal, hypericin, methylene violet, proflavine, rivanol, acriflavine, toluidine blue, trypan blue, neutral red and mixtures thereof. The photo-oxidant preferably has an antiseptic effect. In certain preferred embodiments, the photo-oxidant comprises

methylene blue. The concentration of methylene blue in the fluid is preferably up to about 1500 mg/100 ml.

In certain embodiments, the anticoagulant comprises a member selected from the group consisting of citrate, heparin, urokinase, tissue plasminogen activation (tPA) and mixtures thereof. In one preferred embodiment, the anticoagulant comprises citrate. In another embodiment, the concentration of citrate in the fluid is at least as high as the calcium concentration in a patient's blood. In still another form of the invention, the concentration of citrate in the fluid is from about 1.5 to about 47% by weight. In yet another embodiment, the concentration of citrate in the fluid is from about 0.01 to about 1.0 Molar.

In one preferred embodiment, the fluid comprises citrate and methylene blue. In another embodiment, the concentration of citrate in the fluid is from about 1.5 to about 23% by weight and the concentration of methylene blue in the fluid is from about 1 to about 1000 mg/100 ml. In a preferred embodiment, the concentration of citrate in the fluid is about 7% by weight and the concentration of methylene blue in the fluid is about 10 mg/100 ml. In one embodiment, the pH of the fluid is from about 4 to about 8. In another embodiment, the pH of the fluid is from about 6 to about 8. In another embodiment, the pH of the fluid is about 7.2. In another embodiment, the relative density of the fluid is from about 1.000 to about 1.080 g/ml. In another embodiment, the relative density of the fluid is from about 1.035 to about 1.045 g/ml.

In yet another embodiment, the fluid further comprises a viscosifying agent. The viscosifying agent can be, for example, a member selected from the group

consisting of dextran, polyethylene glycol, glycerin, polygeline, and non-metabolizable sugars such as sorbitol and mannitol and mixtures of these compounds.

In another embodiment, the photo-oxidant features  
5 a readily detectible color, thereby allowing healthcare professionals to readily recognize the fluid, avoiding accidental infusion of the fluid into a patient's bloodstream.

In another aspect of the invention, there is  
10 provided a method for treating a patient. The method includes: (1) selecting a patient having an indwelling catheter defining a lumen therethrough; and (2) infusing an inventive aqueous catheter lock solution into the lumen, the solution comprising an anticoagulant and a  
15 photo-oxidant, wherein the solution has a density of from about 1.000 to about 1.3000 g/ml.

In another form, the invention provides a method of inhibiting infections in an animal having an indwelling catheter defining at least one lumen  
20 therethrough, said method comprising infusing into the lumen a pharmaceutically acceptable lock solution in accordance with the invention including an anticoagulant and a photo-oxidant, wherein said lock solution has a density and a viscosity effective to  
25 maintain a substantial portion of the lock solution in said lumen for at least about 8 hours. In certain embodiments, the method also includes exposing the photo-oxidant to light.

The invention also provides a method of treating  
30 animals having a surgically implanted catheter. This method comprises infusing into said catheter a pharmaceutically acceptable lock solution comprising methylene blue in concentration of from about 1

mg/100ml to about 100 mg/100ml. In one embodiment, the catheter is selected from the group consisting of an intravascular catheter and a body cavity catheter. In another embodiment, the lumen of the catheter has an internal volume and said infusing includes infusing an amount of the lock solution of from about 80% to about 120% of the internal volume.

In another form of the invention, there is provided an infusion device for infusing a lock solution into a lumen of a catheter. The device includes: (1) a syringe; and (2) a pharmaceutically acceptable lock solution in accordance with the invention contained within the syringe; wherein the syringe containing the lock solution is sterilized.

Also provided is a kit for locking a patient's catheter. The kit includes: (1) a container having therein an inventive catheter lock solution; (2) a syringe with Luer lock tip; (3) a replacement cap; and (4) a needleless single-dose vial access spike with dead cap.

The invention will be further described with reference to the following specific Examples. It will be understood that these Examples are also illustrative and not restrictive in nature.

#### EXAMPLE 1

FIG. 2 is a representation of the effect of methylene blue (12 mg/100ml) on concentration of a gram negative organism, Escherichia Coli, without light exposure. All E. Coli are killed within one day. It is expected that illumination will augment bacterial killing by methylene blue even more.

**EXAMPLE 2**

Fig 3 is a representation of the effect of methylene blue (12 mg/100ml) on concentration of a gram positive organism, Enterobacter Faecalis, without light exposure.

- 5 All Enterobacter are killed within one day. It is expected that illumination will augment bacterial killing by methylene blue even more.

**EXAMPLE 3**

10 **Manufacturing of a Representative Catheter Lock Solution**

**Method**

- A catheter lock solution is formulated as a sterile mixture of USP grade chemicals in the following concentrations: 0.24 M citrate buffer solution and  
15 0.01% (W/V) methylene blue. The solution is designed to have a relative density of 1.035 to 1.045, and pH of 7.1-7.3. The citrate buffer solution is prepared at the desired pH (7.1-7.3) by mixing one liter of 0.24 M  
20 trisodium citrate dihydrate solution (70.58g/L) and 6.5 ml of 0.24 M anhydrous citric acid solution (46.10 g/L). The final solution is obtained by adding 0.0117 grams (11.7 mg) of methylene blue trihydrate per 100 ml of citrate buffer solution in the actual batch size.  
25 The solution is stored at room temperature; however, brief exposure up to 50° C (122° F) does not adversely affect the product.

- The bulk solution is then pumped into an aseptic filling area, passing through a secondary and then  
30 primary 0.2 micron sterilizing filter before flowing into a sterilized surge type or pressure type vessel. The sterilized solution in the sterile vessel flows to the filler where light resistant, type 1 glass vials (5



mL, Kimble, type 1 Borosilicate Glass Amber Vial, 13-mm Finish, Untreated) are conveyed and filled with the predetermined fill volume. The filled vials are then conveyed to the stoppering location where stoppers  
5 (West, 13 mm, 4432/50 Rubber Stopper) are placed in the vials. The vials are then conveyed to a capping machine which applies aluminum crimp seals with flip off caps to each vial (West, 13 mm Aluminum Seal, Flip-off Button). Overseals (crimped caps) are applied in a  
10 capping area outside of the aseptic processing area.

The filled, stoppered and capped vials are then inspected for visible particulate matter and other defects.

#### 15 **Suppliers**

The starting materials for making the solution of this embodiment are readily available commercially, and can be obtained from the sources identified in Table III:

20

**Table III**

Chemical Name	Supplier	Concentration
Citric Acid Anhydrous, USP	Spectrum Lab Product 14422 South San Pedro St. Gardena, CA 90248	USP
Sodium Citrate, Tri basic Dihydrate, USP	Sigma-Aldrich 3050 Spruce St. St. Louis, MO 63103	USP
Methylene Blue, USP	Spectrum Lab Product 14422 South San Pedro St. Gardena, CA 90248	USP
WFI, USP	Contract Mfg	USP

**EXAMPLE 4**

The antimicrobial effectiveness after one day and three days of the citrate/methylene blue catheter lock solution described in Example 3 was tested under USP procedures (10 mL sample). Results are shown in Table IV below:

**TABLE IV**

Organism	Day Zero	Day 1	Day 3
<i>Escherichia coli</i>	$1.1 \times 10^5$	$6.7 \times 10^3$	$1.9 \times 10^4$
<i>Pseudomonas aeruginosa</i>	$1.5 \times 10^5$	$1.9 \times 10^3$	$4.1 \times 10^4$
<i>Candida albicans</i>	$1.6 \times 10^5$	$3.8 \times 10^5$	$3.6 \times 10^5$
<i>Staphylococcus aureus</i>	$8.3 \times 10^2$	$5.0 \times 10^0$	$<1.0 \times 10^0$
<i>Aspergillus niger</i>	$2.5 \times 10^5$	$3.4 \times 10^5$	$3.7 \times 10^5$

The conclusion of this test is that the solution achieved a 1.0 log kill for bacteria and no change for fungi at one (1) day. *Staphylococcus Aureus* experienced an immediate 3 log kill upon inoculation.

**Example 5**

As part of a shelf life study, antimicrobial effectiveness of the solution described in Example 3 was tested after one day and three days under USP procedures (2 mL sample) using three bacteria and one fungus. This study was conducted 45 days after production. The results of this study are shown in Table V below:

**TABLE V**

Organism	Day Zero	Day 1	Day 3
<i>Escherichia coli</i>	$1.4 \times 10^5$	$2.9 \times 10^3$	$1.0 \times 10^2$
<i>Pseudomonas aeruginosa</i>	$4.1 \times 10^5$	$3.0 \times 10^2$	$2.5 \times 10^5$
<i>Candida albicans</i>	$1.4 \times 10^6$	$6.8 \times 10^4$	$2.5 \times 10^4$
<i>Staphylococcus aureus</i>	$7.5 \times 10^4$	$<1.0$	$<1.0$

The conclusion is that there was no decline in antimicrobial effectiveness of the solution following 45 days of storage at room temperature.

5

**EXAMPLE 6**

The catheter lock solution is removed before each dialysis procedure, by attaching a syringe to each catheter lumen and removing 1 mL more than the catheter lumen volume (about 3 mL total), discarding the  
10 syringe, then flushing the catheter with 5 mL of sterile normal saline.

At the end of the patient's hemodialysis treatment each lumen of the catheter is filled with the lock solution in an amount equal to the fill volume of the  
15 catheter lumen. Each lumen is filled to the tip using a quick bolus technique for the first 2/3 of the injected volume, and slow infusion (over 10 seconds) for the last 1/3 of the injected volume.

While the invention has been illustrated and  
20 described in detail in the drawings and foregoing description, the same is to be considered as illustrative and not restrictive in character, it being understood that only the preferred embodiments have been shown and described and that all changes and  
25 modifications that come within the spirit of the invention are desired to be protected.

What is claimed is:

1. An aqueous catheter lock fluid comprising an anticoagulant and a photo-oxidant, wherein the fluid has a density of from about 1.000 to about 1.300 g/ml.

5

2. The fluid according to claim 1 wherein the photo-oxidant comprises a member selected from the group consisting of methylene blue, Rose Bengal, hypericin, methylene violet, proflavine, rivanol, acriflavine, toluidine blue, trypan blue, neutral red and mixtures thereof

10

3. The fluid according to any of claims 1 and 2 wherein the photo-oxidant has an antiseptic effect.

15

4. The fluid according to claim 1 wherein the photo-oxidant comprises methylene blue.

5. The fluid according to claim 4 wherein the concentration of methylene blue in the fluid is up to about 1500 mg/100 ml.

20

6. The fluid according to claim 4 wherein the concentration of methylene blue in the fluid is from about 1 to about 1500 mg/100 ml.

25

7. The fluid according to claim 4 wherein the concentration of methylene blue in the fluid is from about 1 to about 1000 mg/100 ml.

30

8. The fluid according to claim 4 wherein the concentration of methylene blue in the fluid is from about 1 to about 100 mg/100 ml.

9. The fluid according to claim 4 wherein the concentration of methylene blue in the fluid is from about 1 to about 50 mg/100 ml.

5

10. The fluid according to claim 4 wherein the concentration of methylene blue in the fluid is about 10 mg/100 ml.

10 11. The fluid according to any of claims 1-10 wherein the anticoagulant comprises a member selected from the group consisting of citrate, heparin, urokinase, tissue plasminogen activation (tPA) and mixtures thereof.

15

12. The fluid according to any of claims 1-10 wherein the anticoagulant comprises a member selected from the group consisting of citrate and heparin.

20 13. The fluid according to any of claims 1-10 wherein the anticoagulant comprises citrate.

14. The fluid according to claim 13 wherein the concentration of citrate in the fluid is at least as  
25 high as the calcium concentration in a patient's blood.

15. The fluid according to claim 13 wherein the concentration of citrate in the fluid is from about 1.5 to about 47% by weight.

30

16. The fluid according to claim 13 wherein the concentration of citrate in the fluid is from about 1.5 to about 23% by weight.

17. The fluid according to claim 13 wherein the concentration of citrate in the fluid is from about 1.5 to about 15% by weight.

5

18. The fluid according to claim 13 wherein the concentration of citrate in the fluid is about 7% by weight.

10 19. The fluid according to claim 13 wherein the concentration of citrate in the fluid is from about 0.01 to about 1.0 Molar.

20. The fluid according to claim 4 wherein the  
15 concentration of citrate in the fluid is from about 0.1 to about 0.5 Molar.

21. The fluid according to claim 4 wherein the concentration of citrate in the fluid is about 0.24  
20 Molar.

22. The fluid according to claim 1 wherein the fluid comprises citrate and methylene blue.

25 23. The fluid according to claim 22 wherein the concentration of citrate in the fluid is from about 1.5 to about 23% by weight and wherein the concentration of methylene blue in the fluid is from about 1 to about 1000 mg/100 ml.

30

24. The fluid according to claim 22 wherein the concentration of citrate in the fluid is from about 1.5 to about 15% by weight and wherein the concentration of

methylene blue in the fluid is from about 1 to about 100 mg/100 ml.

25. The fluid according to claim 22 wherein the  
5 concentration of citrate in the fluid is about 7% by weight and wherein the concentration of methylene blue in the fluid is about 10 mg/100 ml.

26. The fluid according to any of claims 1-25  
10 wherein the pH of the fluid is from about 4 to about 8.

27. The fluid according to any of claims 1-25 wherein the pH of the fluid is from about 4.5 to about 8.

15 28. The fluid according to any of claims 1-25 wherein the pH of the fluid is from about 6 to about 8.

29. The fluid according to any of claims 1-25 wherein the pH of the fluid is from about 7.0 to about 7.4.

20

30. The fluid according to any of claims 1-25 wherein the pH of the fluid is about 7.2.

31. The fluid according to any of claims 1-30  
25 wherein the relative density of the fluid is from about 1.000 to about 1.080 g/ml.

32. The fluid according to any of claims 1-30 wherein the relative density of the fluid is from about  
30 1.030 to about 1.050 g/ml.

33. The fluid according to any of claims 1-30 wherein the relative density of the fluid is from about 1.035 to about 1.045 g/ml.

5        34. The fluid according to any of claims 1-33, further comprising a viscosifying agent.

35. The fluid according to any of claims 1-33, further comprising a member selected from the group  
10 consisting of dextran, polyethylene glycol, glycerin, polygeline, and non-metabolizable sugars such as sorbitol and mannitol and mixtures of these compounds.

36. The fluid according to any of claims 1-35,  
15 wherein the photo-oxidant features a readily detectible color, thereby allowing healthcare professionals to readily recognize the fluid, avoiding accidental infusion of the fluid into a patient's bloodstream.

20        37. The fluid according to any of claims 1-36 wherein the anticoagulant comprises heparin in a concentration of from about 100 units/ml to about 10,000 units/ml.

25        38. A method for treating a patient, comprising:  
         selecting a patient having an indwelling catheter defining a lumen therethrough;  
         infusing an aqueous catheter lock solution  
         into the lumen, the solution comprising an  
30 anticoagulant and a photo-oxidant, wherein the solution has a density of from about 1.000 to about 1.3000 g/ml.



39. A method of inhibiting infections in an animal having an indwelling catheter defining at least one lumen therethrough, said method comprising infusing into the lumen a pharmaceutically acceptable lock solution including an anticoagulant and a photo-oxidant, wherein said lock solution has a density and a viscosity effective to maintain a substantial portion of the lock solution in said lumen for at least about 8 hours.

10

40. The method according to any of claims 38 and 39 wherein the photo-oxidant comprises a member selected from the group consisting of methylene blue, Rose Bengal, hypericin, methylene violet, proflavine, rivanol, acriflavine, toluidine blue, trypan blue, neutral red and mixtures thereof

20

41. The method according to any of claims 38-40 wherein the photo-oxidant has an antiseptic effect.

42. The method according to any of claims 38-41 wherein the photo-oxidant comprises methylene blue.

43. The method according to any of claims 38-42, wherein the photo-oxidant features a readily detectible color, thereby allowing healthcare professionals to readily recognize the fluid, avoiding accidental infusion of the fluid into a patient's bloodstream.

44. The method of any of claims 38 to 43, further comprising exposing the photo-oxidant to light.

45. The method of any of claims 38 to 44 wherein the photo-oxidant has antibacterial activity.

46. A method of treating animals having a  
5 surgically implanted catheter, said method comprising infusing into said catheter a pharmaceutically acceptable lock solution comprising methylene blue in concentration of from about 1 mg/100ml to about 100 mg/100ml.

10

47. The method according to any of claims 38-46 wherein the concentration of methylene blue in the solution is up to about 1500 mg/100 ml.

15 48. The method according to any of claims 38-46 wherein the concentration of methylene blue in the solution is from about 1 to about 1500 mg/100 ml.

49. The method according to any of claims 38-46  
20 wherein the concentration of methylene blue in the solution is from about 1 to about 1000 mg/100 ml.

50. The method according to any of claims 38-46 wherein the concentration of methylene blue in the  
25 solution is from about 1 to about 100 mg/100 ml.

51. The method according to any of claims 38-46 wherein the concentration of methylene blue in the solution is from about 1 to about 50 mg/100 ml.

30

52. The method according to any of claims 38-46 wherein the concentration of methylene blue in the solution is about 10 mg/100 ml.

53. The method according to any of claims 38-52 wherein the anticoagulant comprises a member selected from the group consisting of citrate, heparin,  
5 urokinase, tissue plasminogen activation (tPA) and mixtures thereof.

54. The method according to any of claims 38-52 wherein the anticoagulant comprises a member selected  
10 from the group consisting of citrate and heparin.

55. The method according to any of claims 38-52 wherein the anticoagulant comprises citrate.

15 56. The method according to any of claims 38-55 wherein the concentration of citrate in the solution is at least as high as the calcium concentration in a patient's blood.

20 57. The method according to any of claims 38-55 wherein the concentration of citrate in the solution is from about 1.5 to about 47% by weight.

58. The method according to any of claims 38-55  
25 wherein the concentration of citrate in the solution is from about 1.5 to about 23% by weight.

59. The method according to any of claims 38-55 wherein the concentration of citrate in the solution is  
30 from about 1.5 to about 15% by weight.

60. The method according to any of claims 38-55 wherein the concentration of citrate in the solution is about 7% by weight.

5 61. The method according to any of claims 38-55 wherein the concentration of citrate in the solution is from about 0.01 to about 1.0 Molar.

62. The method according to any of claims 38-55  
10 wherein the concentration of citrate in the solution is from about 0.1 to about 0.5 Molar.

63. The method according to any of claims 38-55 wherein the concentration of citrate in the solution is  
15 about 0.24 Molar.

64. The method according to any of claims 38-63 wherein the solution comprises citrate and methylene blue.  
20

65. The method according to claim 64 wherein the concentration of citrate in the solution is from about 1.5 to about 15% by weight and wherein the concentration of methylene blue in the solution is from  
25 about 1 to about 1000 mg/100 ml.

66. The method according to claim 64 wherein the concentration of citrate in the solution is from about 1.5 to about 15% by weight and wherein the  
30 concentration of methylene blue in the solution is from about 1 to about 100 mg/100 ml.

67. The method according to claim 64 wherein the concentration of citrate in the solution is about 7% by weight and wherein the concentration of methylene blue in the solution is about 10 mg/100 ml.

5

68. The method according to any of claims 38-67 wherein the pH of the solution is from about 4 to about 8.

10

69. The method according to any of claims 38-67 wherein the pH of the solution is from about 4.5 to about 8.

15

70. The method according to any of claims 38-67 wherein the pH of the solution is from about 6 to about 8.

20

71. The method according to any of claims 38-67 wherein the pH of the solution is from about 7.0 to about 7.4.

72. The method according to any of claims 38-67 wherein the pH of the solution is about 7.2.

25

73. The method according to any of claims 38-72 wherein the relative density of the solution is from about 1.000 to about 1.080 g/ml.

30

74. The method according to any of claims 38-72 wherein the relative density of the solution is from about 1.030 to about 1.050 g/ml.

75. The method according to any of claims 38-72 wherein the relative density of the solution is from about 1.035 to about 1.045 g/ml.

5        76. The method according to any of claims 38-75 wherein the solution further comprises a viscosifying agent.

77. The method according to any of claims 38-75  
10 wherein the solution further comprises a member selected from the group consisting of dextran, polyethylene glycol, glycerin, polygeline, and non-metabolizable sugars such as sorbitol and mannitol and mixtures of these compounds.

15

78. The method according to any of claims 38-75 wherein the anticoagulant comprises heparin in a concentration of from about 100 units/ml to about 10,000 units/ml.

20

79. The method of any of claims 38 to 78 wherein the catheter is selected from the group consisting of an intravascular catheter and a body cavity catheter.

25        80. The method of any of claims 38 to 79 wherein the lumen of the catheter has an internal volume and said infusing includes infusing an amount of the lock solution of from about 80% to about 120% of the internal volume.

30

81. An infusion device for infusing a lock solution into a lumen of a catheter, said device comprising:

a syringe;  
a pharmaceutically acceptable lock solution  
contained within the syringe, said lock solution  
including an anticoagulant and a photo-oxidant;  
5 wherein said syringe containing the lock solution  
is sterilized.

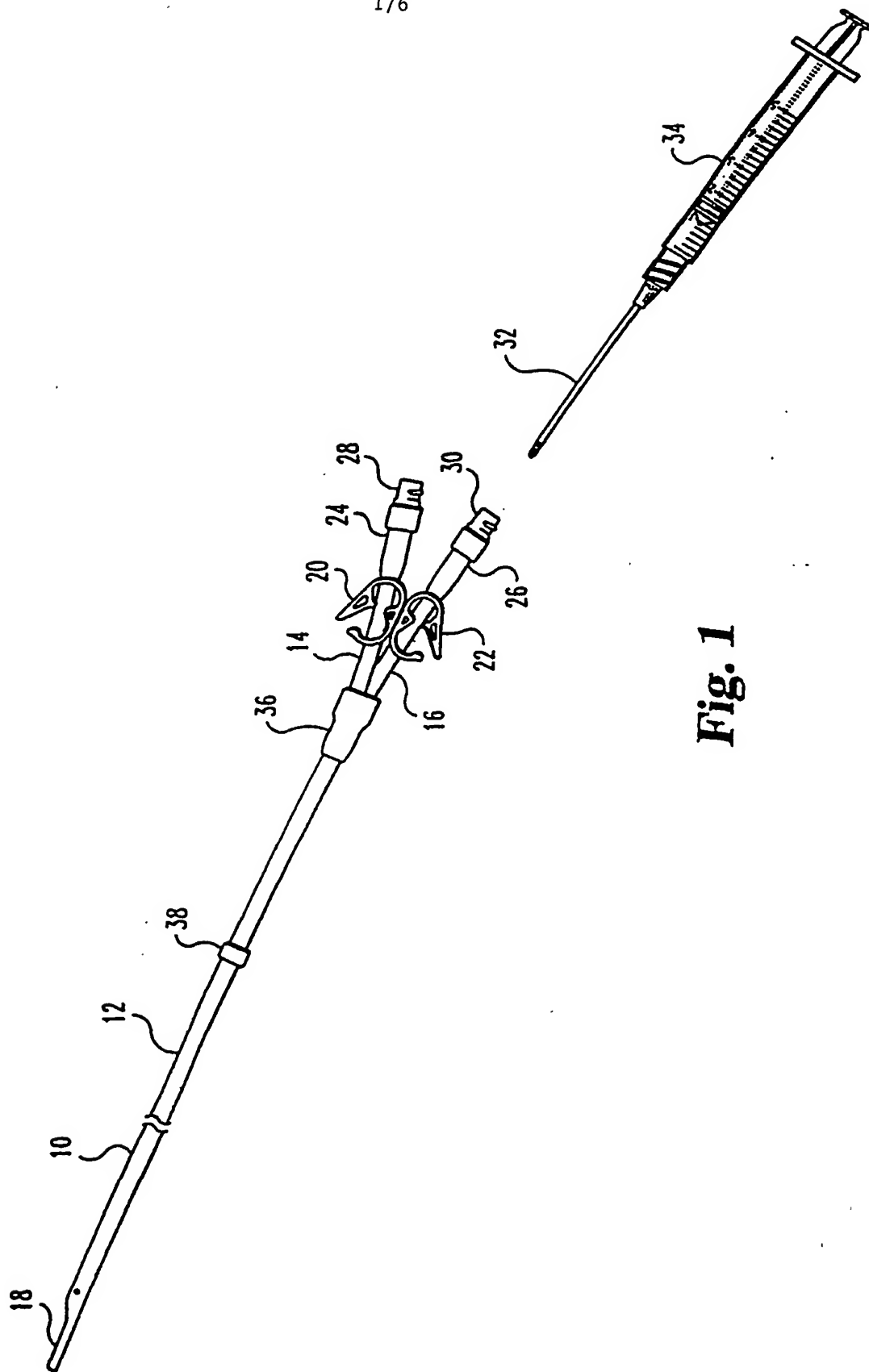
82. The device of claim 81, wherein the photo-  
oxidant comprises methylene blue.  
10

83. The device of any of claims 81 and 82 wherein  
the anticoagulant comprises citrate.

84. The device of any of claims 81 and 82 wherein  
15 the lock solution comprises a viscosifying agent  
selected from polyethylene glycol, glycerin, polygeline  
and mixtures thereof.

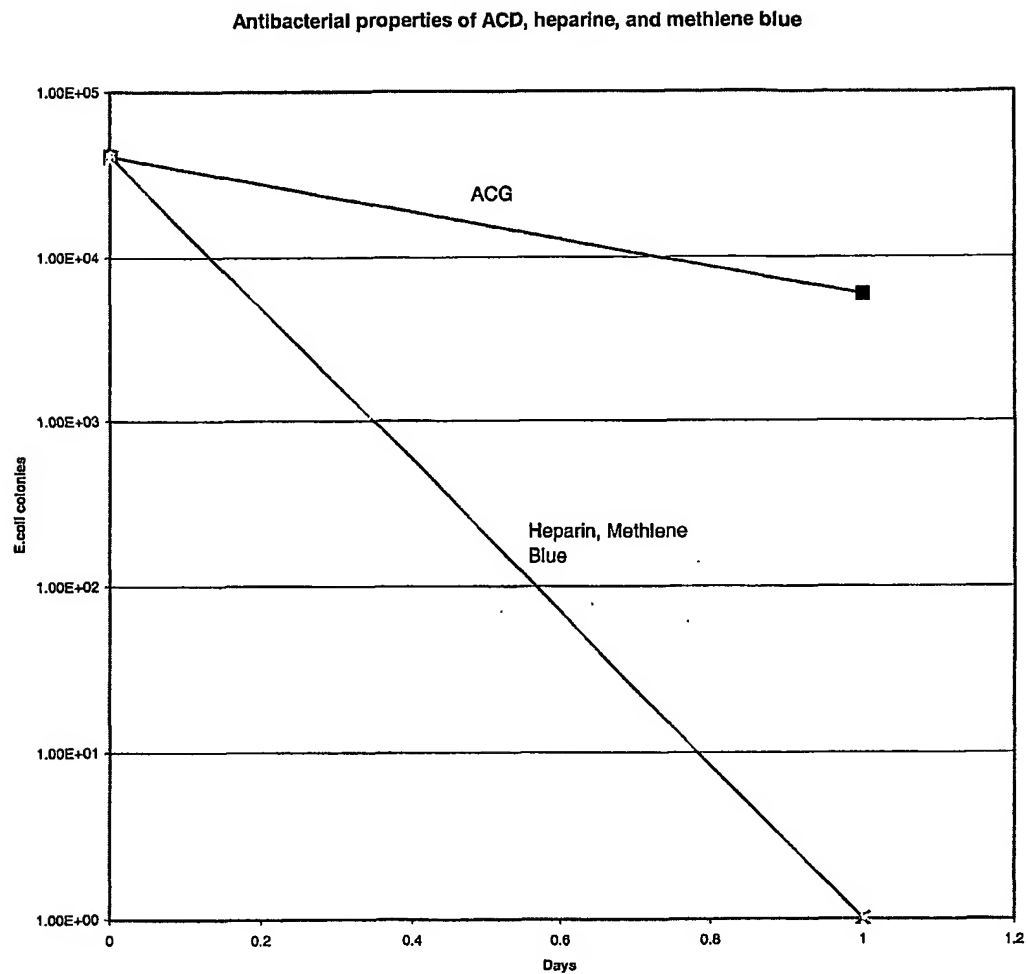
85. A kit for locking a patient's catheter,  
20 comprising:  
a container having therein a catheter lock  
solution, the catheter lock solution comprising an  
anticoagulant and a photo-oxidant, and having a density  
of from about 1.000 to about 1.3000 g/ml;  
25 a syringe with Luer lock tip;  
a replacement cap; and  
a needleless single-dose vial access spike with  
dead cap.

86. The kit according to claim 85 wherein the  
30 solution comprises citrate and methylene blue.



**Fig. 1**



**Figure 2**

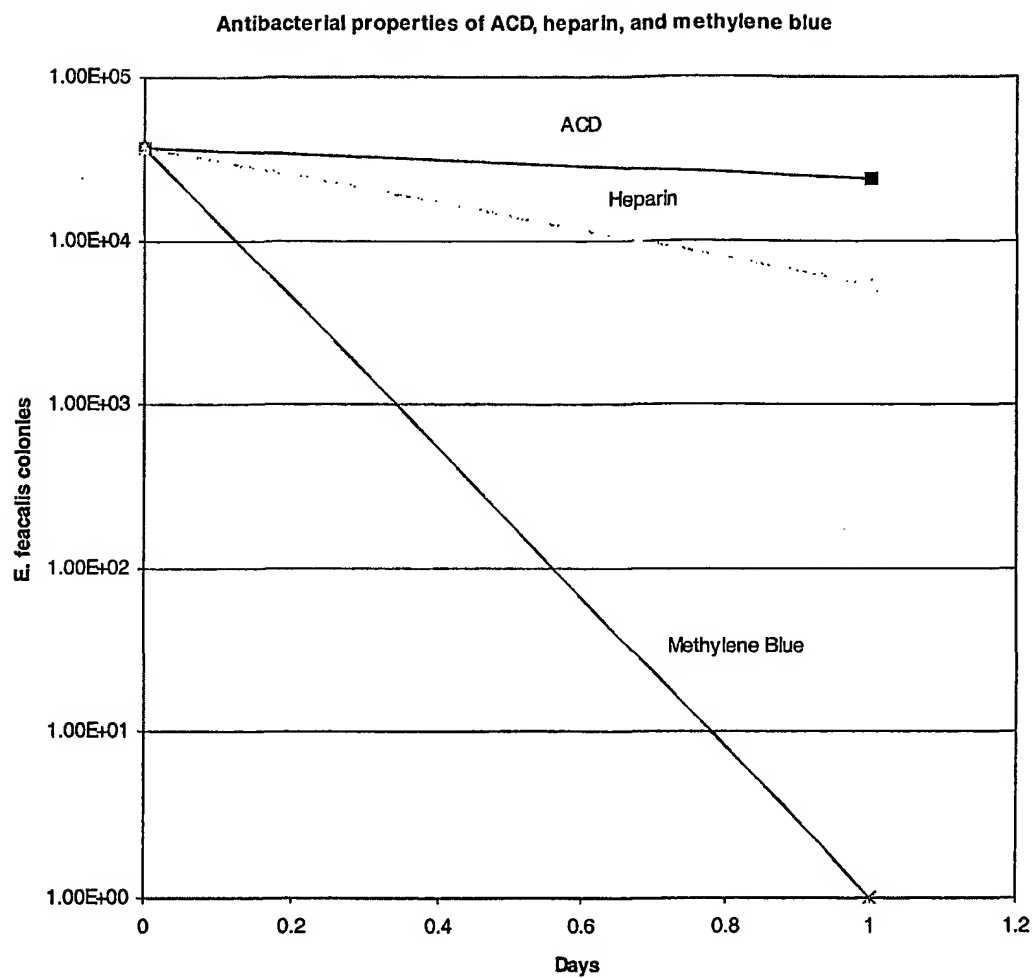
**Figure 3**

Figure 4: Antibacterial properties of methylene blue 0.01% in ACD (4% citrate) for gram positive organisms and gram negative organisms.

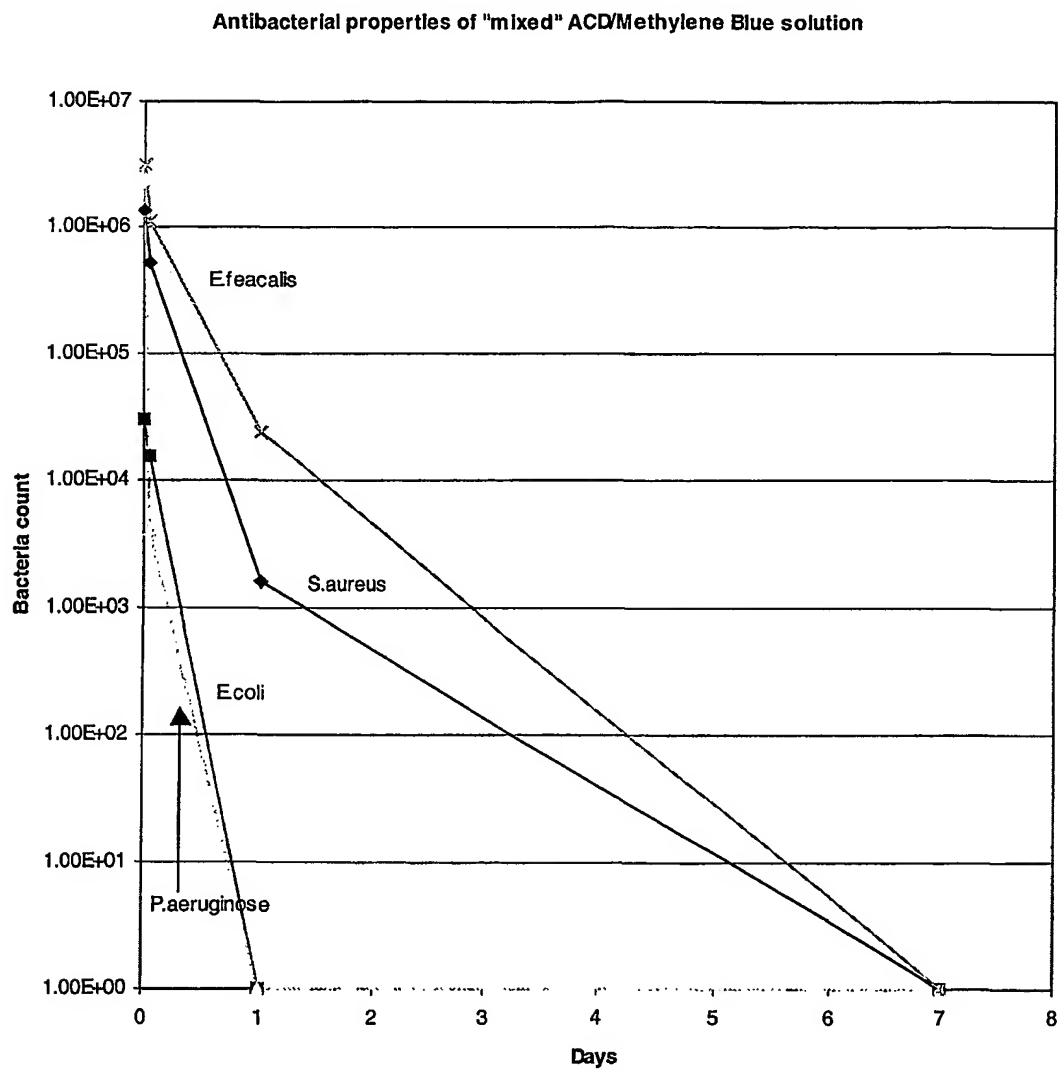


Figure 4

Figure 5: Antiseptic properties of methylene blue 0.01% in 0.24 Molar citrate buffer at pH 4.5 and 7.2 for gram-positive organisms and gram-negative organisms.

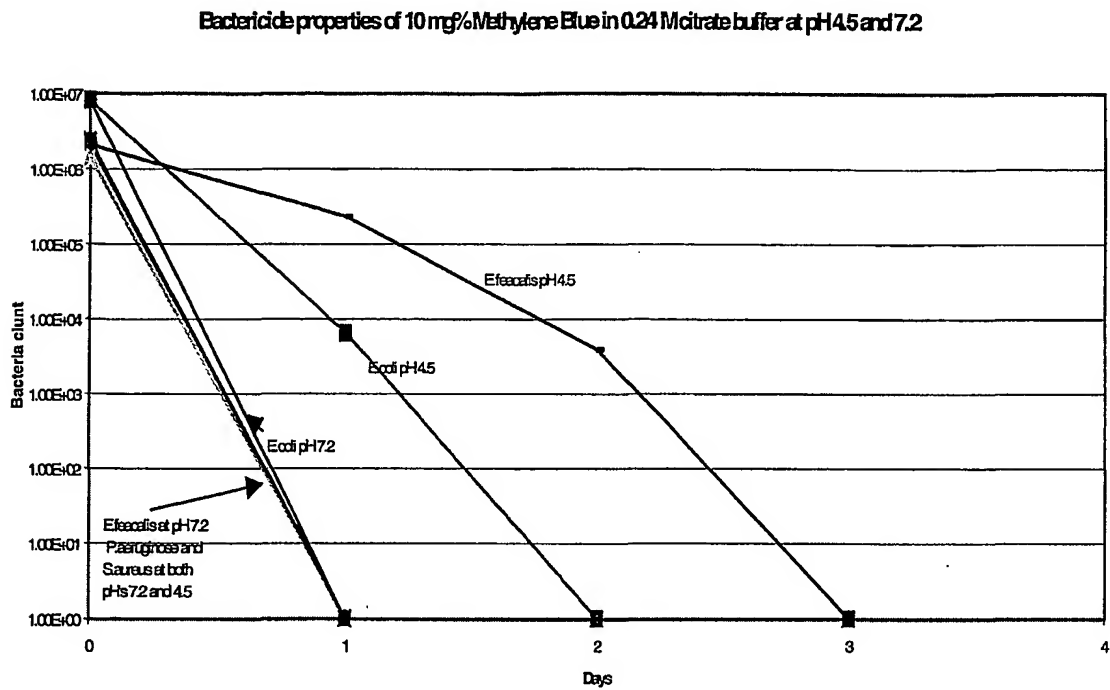
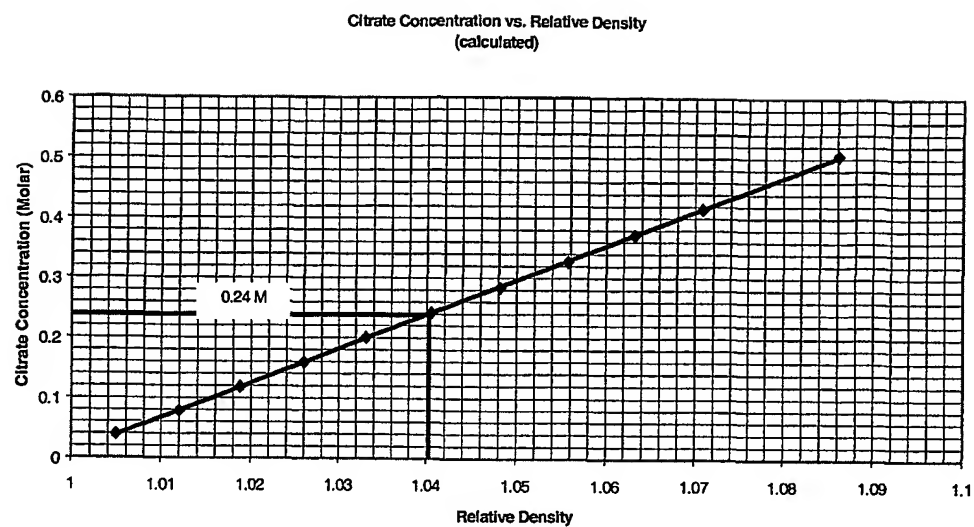


Figure 5

**Figure 6**

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/15177

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61M 31/00

US CL : 604/508

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 604/508, 43,48, 500, 93.01, 264-267, 269, 523, 288.01,890.1,891.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
east/brs - anticoagulant and photo-oxidant, heparin , citrate, methylene blue

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/10385 A1 ( ASH ) 02 March 2000, see entire patent.	1-2,4-10,20-25,38-39,46,81-83,85-86
A, P	US 6,207,107 B1 (DEBRAUWERE et al.) 27 March 2001, seen entire patent.	1-2,4-10,20-25,38-39,46,81-83,85-86
A	US 5,002,965 A ( RAMWELL et al.) 26 March 1991, see entire patent.	1-2,4-10,20-25,38-39,46,81-83,85-86

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"B" earlier application or patent published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"I" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

13 August 2001 (13.08.2001)

Date of mailing of the international search report

05 SEP 2001

Name and mailing address of the ISA/US

Commissioner of Patents and Trademarks

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# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/15177

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claim Nos.: 3,11-19,26-37,40-45,47-80 and 84  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐  
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.